# Valproic acid

**Brand Name: Depakene**
**Drug Class: Opportunistic Infection and Other Drugs**

## Drug Description

Valproic acid is a carboxylic acid that increases gamma-amino butyric acid (GABA) levels in the central nervous system and inhibits the enzyme histone deacetylase 1 (HDAC1). [1]

## HIV/AIDS-Related Uses

Valproic acid may be useful in the treatment of HIV infection by reducing the number of dormant infected T cells, making the virus more accessible to attack by other antiretrovirals.[2] [3]

## Non-HIV/AIDS-Related Uses

Valproic acid is an anticonvulsant indicated for use as monotherapy and adjunctive therapy in the treatment of simple or complex absence seizures.[4] Valproic acid has been studied in the treatment of manic episodes associated with bipolar disorder and in migraine headache prophylaxis, although it has not been approved by the FDA for these disorders.[5]

## Pharmacology

Valproic acid, a histone deacetylase (HDAC)-1 inhibitor, stimulates the release of HIV from latent T cells, allowing existing antiretrovirals to attack the re-emerged virus. HDAC-1 inhibition may suppress HIV promoter activity in latent T cells infected with the virus.

In a small proof-of-concept study, valproic acid administered to HIV infected adults for 3 months with enfuvirtide accelerated the clearance of HIV from latent T cells and decreased the frequency of latent cell infection significantly in 3 of 4 patients. These findings suggest valproic acid may be useful in decreasing the HIV reservoir and eliminating more of the virus from infected cells.[6] [7]

Valproic acid dissociates to the active valproate ion in the gastrointestinal (GI) tract. Absorption from the GI tract varies with dosage regimens and formulations, but the variances are unlikely to have a clinical effect.

Valproic acid is protein bound in a concentration-dependent manner; the free fraction increases from 10% to nearly 20% at 40 mcg/ml and 130 mcg/ml concentrations, respectively. Cerebrospinal fluid concentrations approximate the unbound plasma concentrations at 10%. Protein binding is saturable; unbound valproic acid pharmacokinetic measurements are linear. Mean terminal half-life ranges from 9 to 16 hours.

Valproic acid is almost entirely hepatically metabolized. Nearly 40% of a dose is glucuronidated, and mitochondrial beta-oxidation accounts for more than 40% of the dose. Other oxidative metabolism accounts for the remaining administered drug. Less than 3% of drug is recovered unchanged. Children between the ages of 3 months and 10 years have 50% higher clearance rates. Elderly clearance rates are reduced by 39% to 44%.[8]

Valproic acid is in FDA Pregnancy Category D. The drug may be teratogenic in humans. Neural tube defects and other congenital anomalies may occur, and clotting abnormalities may develop in pregnant women.[9]

## Adverse Events/Toxicity

In the first proof-of-concept study of valproic acid in HIV infected patients, no severe adverse effects occurred. Mild anemia and irritation at injection sites were attributed to concomitant antiretrovirals.[10]

Hepatic failure resulting in fatalities has occurred in people taking valproic acid, usually within the first 6 months of treatment. Hepatotoxicity may be preceded by symptoms of malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Valproic acid should be discontinued immediately in the presence of suspected or apparent hepatic dysfunction; dysfunction may progress despite drug discontinuation.[11]

Adverse effects commonly associated with divalproex sodium, an oral salt dosage form of valproic acid, include headache; asthenia; nausea, vomiting, abdominal pain, and diarrhea;

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## Adverse Events/Toxicity (cont.)

somnolence; dizziness; and tremor. Photosensitivity, Steven-Johnsons Syndrome, and rare cases of toxic epidermal necrosis have occurred. Minor, dose-related elevations of hepatic enzymes occur frequently.[12]

## Drug and Food Interactions

Food does not appear to alter clinical effects of valproic acid, although single dose half-lives appear increased by 4 hours when the drug is administered with food.[13]

Valproic acid may interact with concurrently administered medications capable of hepatic enzyme induction; for example, phenytoin, cyclobenzaprine, and phenobarbital can double valproic acid clearance. Cytochrome P450 inhibitors have a smaller effect on valproic acid clearance, because CYP-mediated oxidation of valproic acid is secondary to glucuronidation and beta-oxidation.[14]

Valproic acid is a weak inhibitor of some hepatic enzymes and is able to displace plasma protein-bound drugs. These effects increase the serum levels of cyclobenzaprine, diazepam, phenobarbital, phenytoin, and some other medications.

Concurrent valproic acid and zidovudine administration results in a 38% decrease in zidovudine clearance but half-life is unaffected.

Coadministration of valproic acid and aspirin results in a fourfold increase in the free fraction of valproic acid, compared to monotherapy due to inhibition of beta-oxidation.[15]

## Contraindications

Valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction. Valproic acid is contraindicated in patients with known hypersensitivity to the drug.[16]

## Clinical Trials

For information on clinical trials that involve Valproic acid, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Valproic acid AND HIV Infections.

## Dosing Information

Mode of Delivery: Oral.[17]

Dosage Form: Orange-colored, soft gelatin capsules containing valproic acid 250 mg. Red-colored syrup containing valproic acid 250 mg as a sodium salt per 5 ml.[18]

Doses of 500 to 750 mg twice daily have been tested for use in combination with enfuvirtide and certain antiretroviral regimens.[19]

Storage: Store capsules at 15 C to 25 C (59 F to 77 F). Store syrup below 30 C (86 F).[20]

## Chemistry

CAS Name: 2-propylpentanoic acid[21]

CAS Number: 99-66-1[22]

Molecular formula: C8-H16-O2[23]

C67%, H11%, O22%[24]

Molecular weight: 144[25]

Physical Description: Valproic acid is a colorless liquid with a characteristic odor.[26]

Solubility: Valproic acid is slightly soluble in water at 1.3 mg/ml and is very soluble in organic solvents.[27]

## Other Names

VPA[28]

Acido valproico[29]

Valproate[30]

Depakote[31]

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## Other Names (cont.)

Divalproex sodium[32]

## Further Reading

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Use of Valproic Acid to Purge HIV From Resting CD4+ Memory Cells. Available at: http://clinicaltrials.gov/ct/show/NCT00289952.

## Manufacturer Information

Valproic acid
Abbott Laboratories
One Hundred Abbott Park Rd
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## For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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## References


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